REMARKS

Claims 1-28 were pending in the present application. Claims 1-9 and 14-28 have been canceled, without prejudice, as being directed to a non-elected invention. Claim 13 has also been canceled, without prejudice. Claims 9 and 12 have been amended, and new claims 29-35 have been added. Accordingly, after the amendments presented herein have been entered, claims 9-12 and 29-35 will remain pending.

Support for the new claims and the claim amendments presented herein can be found throughout the specification, including the originally filed claims. Specifically, Support for new claims 29 and 30 may be found at least, for example, at page 26 lines 33-36 of Applicants' specification. Support for new claims 31-34 may be found at least, for example, at page 27, lines 1-6 of Applicants' specification.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Status of Claims

The Examiner has stated that "[c]laims 1-10 and 14-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim....claims 9-13 are ready for examination in the instant application."

Applicants respectfully wish to point out to the Examiner that claims 9 and 10 are not withdrawn from further consideration as Group II, which includes claims 9-13, was elected in response to the Restriction Requirement of April 23, 2003. Therefore, claims 9-13 should be examined.

Information Disclosure Statement

The Examiner has stated that "[t]he information disclosure statement filed June 6, 2003 as Paper No. 11 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Several of the listed references (Al,

A2, A5 and A6) were not present with the IDS. These references have been lined through as not being considered."

Applicants respectfully submit that copies of each of the cited references was included with the Information Disclosure Statement filed on June 6, 2003, as evidenced by the date-stamped return postcard, a copy of which is included herewith. The postcard indicates that copies of each of the 11 references was included with the Information Disclosure Statement.

However, for the Examiner's convenience, copies of references Al, A2, A5 and A6 have been included herewith. Applicants respectfully request that the Examiner consider these references and initial the enclosed replacement PTO-1449 Form.

Rejection of Claims 9-13 Under 35 U.S.C. §101

The Examiner has rejected claims 9-13 under 35 U.S.C. §101 because "the claimed invention lacks patentable utility." In particular, the Examiner is of the opinion that "[a]lthough compounds can potentially be identified by the claimed methods, there is no substantial and/or specific use for the identified compounds. As a result, there can be no substantial and/or specific use for the methods of identifying the compounds." The Examiner indicates that Applicants' specification states that

> a compound that inhibits the interaction between the MSH4 and MSH5 proteins would theoretically be useful as a contraceptive, and a compound that enhances their interaction would theoretically be useful as a fertility drug. This is based upon the knowledge that: (1) MSH4 and MSH5 are both known to participate in meiotic recombination events that are present during spermatogenesis/oogenesis, (2) that the deletion of either protein alone in a mouse model results in sterility, and (3) that the two proteins are capable of interacting with each other in both a mammalian and a yeast two-hybrid system. However, there is no indication in either the prior art or the instant specification that the interaction between the MSH4 and MSH5 proteins is biologically relevant to either meiotic recombination or an effect on fertility. In fact, there is no indication that disrupting or enhancing the interaction between MSH4 and MSH5 will have any useful effect at all. For example, if both proteins were expressed (instead of deleted, either individually or in concert, as in the prior art and the instant specification), there is no indication that meiotic recombination would be prevented or that sterility would be induced. This is simply a presumption that is made because both proteins interact and are involved separately in meiotic

> recombination and fertility. The fact that the proteins have been implicated in meiotic recombination and fertility (by deletion analysis) does not equate to their interaction being relevant to meiotic recombination and fertility. Thus there is no nexus between the interaction of MSH4 and MSH5 and a biological activity, therefore there is not a substantial or specific use for compounds that modulate the interaction between MSH4 and MSH5.

Applicants respectfully traverse the foregoing rejection. It is Applicants' position that the claimed invention has a specific and substantial utility which has clearly been set forth in the instant specification. Furthermore, the asserted utility would have been credible to one of skill in the art at the time of the invention.

Claim 9, as amended, is directed to a method for identifying a compound that modulates the interaction between MSH4 and MSH5, comprising contacting MSH4 with a test compound and determining the ability of said test compound to modulate the interaction between MSH4 and MSH5, thereby identifying a compound that modulates the interaction between MSH4 and MSH5. Claim 10 is directed to a method for identifying a contraceptive compound, comprising contacting MSH4 with a test compound and determining the ability of said test compound to inhibit the interaction between MSH4 and MSH5, thereby identifying a contraceptive compound. New claim 29 is directed to a method for identifying a compound that modulates the interaction between MSH4 and MSH5, comprising contacting a cell expressing MSH4 and MSH5 with a test compound and determining the ability of said test compound to modulate the interaction between MSH4 and MSH5. New claim 30 is directed to a method for identifying a contraceptive compound, comprising contacting a cell expressing MSH4 and MSH5 with a test compound and determining the ability of said test compound to inhibit the interaction between MSH4 and MSH5, thereby identifying a contraceptive compound.

Applicants respectfully submit that the claimed invention is a method for identifying a composition that itself has ***specific*** and ***substantial*** utility. As set forth in the M.P.E.P., section 2107.01(I) "[a] 'specific utility' is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. . .[a] "substantial utility" defines a "real world" use. . . [f]or example, both a therapeutic method of treating a known or newly discovered disease ***and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use.***"

Applicants' specification clearly states that the compositions identified using the claimed methods are capable of modulating meiotic recombination in a cell and are useful as contraceptive compounds (see, for example, page 11, lines 20-23; page 28, lines 3-8; and page 34, lines 34-36 of Applicants' specification). Thus, the asserted utility is a *specific* utility. Furthermore, this asserted utility is a *substantial* utility as it clearly defines a "real world" use, *i.e.,* as a contraceptive. Moreover, "pharmacological or therapeutic inventions that provide any "immediate benefit to the public" satisfy 35 U.S.C. 101" (M.P.E.P. section 2107.01(III); *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980)). The present invention represents a pharmacological or therapeutic invention which would provide immediate benefit to the public, as the compounds identified by the claimed methods would have utility as to effect contraception, as set forth above. Therefore, Applicants' have set forth a *specific and substantial* utility for the claimed invention.

Applicants respectfully submit that the identified utility is credible. In order to evaluate the credibility of an asserted utility, the Examiner must rely on *In re Langer* (503 F.2d 1380, 183 USPQ 288 (CCPA 1974)) which states that:

> [a]s a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope. (Emphasis in original).

Therefore, as set forth in the M.P.E.P, section 2107.2(III)(a), "*Langer* and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. . . [i]f the asserted utility is credible (i.e., believable based on the record or the nature of the invention), a rejection based on "lack of utility" is not appropriate." Furthermore, "to overcome the presumption of truth that an applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility" (M.P.E.P. section 2107.02(III)(A)).

Applicants respectfully submit that there is no reason for one skilled in the art to question to truth or scope of the asserted utility of the instant invention, as set forth in Applicants'

specification, and that the Examiner has failed to establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the asserted utility.

The Examiner states that "there is no indication in either the prior art or the instant specification that the interaction between the MSH4 and MSH5 is biologically relevant to either meiotic recombination or an effect on fertility." Applicants respectfully submit that Applicants' specification provides ample evidence, including working examples, of the interaction between MSH4 and MSH5 and the relevance of this interaction in meiotic recombination and fertility. In order to illustrate the interaction between MSH4 and MSH5, Applicants' specification describes a mammalian two-hybrid assay in which MSH4 and MSH5 are shown to interact. Specifically, Applicants' specification states that the results of the assay, which are presented in Figure 7, "demonstrate that there is an interaction between MSH4 and MSH5, as measured by luciferase (LUC) units" (page 38, lines 19-21 of Applicants' specification). In addition, Example 9 describes a yeast two-hybrid assay which, as shown in Figure 8, demonstrates the specificity of the MSH4/MSH5 interaction and "the suitability for screening inhibitors of the interaction" (page 38, lines 33-35 of Applicants' specification). Furthermore, Applicants' specification, at page 38 in Example 7, states that "[t]he comparison of the meiotic phenotype between *Msh4*$^{-/-}$ and *Msh5*$^{-/-}$ mice revealed that both MutS homologs are required in the early stages of meiosis I and are essential for normal chromosome synapsis during zygonema." *Msh4*$^{-/-}$/ *Msh5*$^{-/-}$ were generated to investigate if mammalian MSH4 and MSH5 function in the same epistasis group and it was found that "[t]he similarity in meiotic phenotype between *Msh5*$^{-/-}$ *and Msh4*$^{-/-}$/ *Msh5*$^{-/-}$ mice indicates that mammalian MSH5 functions upstream of MSH4 within the same epistasis group ***and both are required at the same time in meiosis to ensure proper chromosome synapsis***."

Based on the evidence presented in Applicants' specification regarding the interaction between MSH4 and MSH5 and the role of MSH4 and MSH5 in modulating meiosis, the asserted utility that the compositions identified using the claimed methods are useful as contraceptive compounds would be credible to one of ordinary skill in the art. The Examiner does not provide any evidence that the credibility of the asserted utility would be doubted by one of ordinary skill in the art. Therefore, the Examiner has failed to overcome the presumption of truth to which the Applicants are entitled based on their assertion of the utility of the invention.

As the Examiner is aware, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). "***Instead, evidence will be sufficient, if considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.***" M.P.E.P. §2164.07. Based on the *ample* teachings in Applicants' specification, including working examples regarding the role and importance of the interaction between MSH4 and MSH5 molecules, Applicants respectfully submit that a person of ordinary skill in the art would conclude that Applicants' asserted utility is more likely than not true, which is all that is required under 35 U.S.C. §101.

In view of all of the foregoing, Applicants respectfully submit that the claimed invention has a specific, substantial, and credible utility that would have been readily apparent to one of ordinary skill in the art. Accordingly, Applicant requests reconsideration and withdrawal of the foregoing 35 USC §101 rejection.

Rejection of Claims 9-13 Under 35 U.S.C. §112, First Paragraph

Claims 9-13 are rejected under 35 U.S.C. §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

Applicants respectfully traverse the foregoing rejection and submit that the claimed invention is fully enabled by Applicants' specification so that one of ordinary skill in the art would able to make and use the invention without undue experimentation.

Claim 9, as amended, is directed to a method for identifying a compound that modulates the interaction between MSH4 and MSH5, comprising contacting MSH4 with a test compound and determining the ability of said test compound to modulate the interaction between MSH4 and MSH5, thereby identifying a compound that modulates the interaction between MSH4 and MSH5. Claim 10 is directed to a method for identifying a contraceptive compound, comprising contacting MSH4 with a test compound and determining the ability of said test compound to inhibit the interaction between MSH4 and MSH5, thereby identifying a contraceptive compound. New claim 29 is directed to a method for identifying a compound that modulates the interaction between MSH4 and MSH5, comprising contacting a cell expressing MSH4 and MSH5 with a

test compound and determining the ability of said test compound to modulate the interaction between MSH4 and MSH5. New claim 30 is directed to a method for identifying a contraceptive compound, comprising contacting a cell expressing MSH4 and MSH5 with a test compound and determining the ability of said test compound to inhibit the interaction between MSH4 and MSH5, thereby identifying a contraceptive compound.

The Examiner is of the opinion that

> [i]n order for the invention to be enabled, the skilled artisan must be able to use the invention; in other words, ***the skilled artisan must have the ability to productively use a compound identified by the claimed method, otherwise the skilled artisan would not be apprised of what to use the method for*** (Emphasis added).

Applicants respectfully point out that the present invention is directed to ***methods*** for identifying compounds, rather than the compounds themselves. Applicants' specification provides ample description of how to use the claimed ***methods*** to identify compounds which modulate the interaction between MSH4 and MSH5 and to identify contraceptive compounds (see, for example, page 11, lines 20-23; page 22, line 19 through page 27, line 6; page 28, lines 3-8; and page 34, lines 34-36 of Applicants' specification).

The Examiner is further of the opinion that "there is no explicit or implicit indication that an interaction between these two proteins is necessary for their roles in meiotic recombination" and questions whether there is a direct interaction between MSH4 and MSH5 "as it is still unclear if there is a bridging molecule between MSH4 and MSH5." The Examiner relies on Pochart *et al (J. Biol Chem.* 272:30345-30349, 1997) and states the following:

> MSH4 and MSH5 co-immunoprecipitate and give a positive selection in a two-hybrid system (see for example the Abstract), but also raises the possibility that the interaction is bridged by a third protein (see for example page 30348, right column, last sentence on the page). Significantly, it is also possible that a non-protein molecule, such as DNA, bridges the interaction between the two molecules; this is particularly relevant in this situation, where the two molecules in question are capable of binding to DNA. For instance, it is possible that both molecules bind to a DNA molecule, where they are in proximity to each other, thereby allowing the proteins to be both co-immunoprecipitated and reconstitute the transcription factor necessary to initiate a positive two-hybrid signal.

Applicants respectfully submit that Applicants' specification contains several working examples which illustrate the interaction between MSH4 and MSH5 and the relevance of this interaction in meiosis. For example, Applicants' specification describes a mammalian two-hybrid assay in which MSH4 and MSH5 are shown to interact. Specifically, Applicants' specification states that the results of the assay, which are presented in Figure 7, "demonstrate that there is an interaction between MSH4 and MSH5, as measured by luciferase (LUC) units" (page 38, lines 19-21 of Applicants' specification). In addition, Example 9 describes a yeast two-hybrid assay which, as shown in Figure 8, demonstrates the specificity of the MSH4/MSH5 interaction and "the suitability for screening inhibitors of the interaction" (page 38, lines 33-35 of Applicants' specification).

Furthermore, the pending claims do not require that there is a ***direct*** interaction between MSH4 and MSH5. The claims are directed to methods of identifying compounds which are capable of modulating the interaction between MSH4 and MSH5 and compounds which modulate contraception. ***It is clear from Applicants' specification, including several working examples, that MSH4 and MSH5 interact with each other, either directly or indirectly.*** This interaction is supported by Pochart, *et al.* which states that, with respect to yeast MSH4 and MSH5, "the work presented here confirms that the Msh4 and Msh5 proteins interact."

With respect to the role of the MSH4 and MSH5 proteins in modulation of meiosis, Applicants' specification, at page 38 in Example 7, states that "[t]he comparison of the meiotic phenotype between *Msh4*$^{-/-}$ and *Msh5*$^{-/-}$ mice revealed that both MutS homologs are required in the early stages of meiosis I and are essential for normal chromosome synapsis during zygonema." *Msh4*$^{-/-}$/*Msh5*$^{-/-}$ mice were generated to investigate if mammalian MSH4 and MSH5 function in the same epistasis group and it was found that "[t]he similarity in meiotic phenotype between *Msh5*$^{-/-}$ *and Msh4*$^{-/-}$/*Msh5*$^{-/-}$ mice indicates that mammalian MSH5 functions upstream of MSH4 within the same epistasis group ***and both are required at the same time in meiosis to ensure proper chromosome synapsis.***" This data confirms a nexus between MSH4 activity, including interaction with MSH5, and modulation of meiosis and fertility. Thus, one of ordinary skill in the art, based on the teachings of Applicants' specification, would be able to make and use the claimed invention without undue experimentation. Accordingly, Applicants' respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 9-13 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 13 under 35 U.S.C. §112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that "[i]t is unclear from the specification how one can 'indirectly contact' MSH4 with a test compound. It appears that the compound would either be in contact with MSH4, or not be in contact with MSH4. Because it is unclear what the intermediate between these two options are, the claim is rendered indefinite."

Applicants respectfully traverse the foregoing rejection and respectfully submit that claim 13 is clear and definite. As set forth in Applicants' specification, MSH4 may be directly contacted with a test compound or indirectly contacted with a test compound (see, for example, page 23, lines 1-7 of Applicants' specification). As set forth in Applicants' specification, the claimed assays may be cell-based or cell-free assays (see page 26, lines 33-37 of Applicants' specification). As would be understood by one of ordinary skill in the art, contacting a cell which expresses MSH4 with a test compound is one example of an indirect contact of MSH4 with a test compound. Furthermore, an indirect contact of MSH4 includes contacting a molecule which in turn affects MSH4. However, in an effort to expedite prosecution of the instant application, and in no way acquiescing to the Examiner's rejection of claim 13, Applicants have canceled claim 13, thereby rendering the foregoing rejection moot.

SUMMARY

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,

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